

PERSPECTIVE

Titrating graft-versus-host disease: is it worth a try?

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The optimum graft-versus-host disease (GVHD) management in today's clinical practice remains controversial. There is an enormous heterogeneity among transplanters in their therapeutic decisions for each individual patient with GVHD. Existing guidelines do not always cover many unique clinical scenarios. Consequently, a significant number of allograft recipients fail either because of severe GVHD or relapse of underlying malignancy. Until more effective methods are available, tailoring the current GVHD management by modification of immunosuppressive therapy in each patient based on disease and transplant characteristics may decrease the mortality. The purpose of this review is to raise several questions among readers about GVHD management and generate new hypotheses, which may need to be tested in cooperative group studies.

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mortality remains challenging. We prevent and treat GVHD based on published guidelines. However, there is tremendous variation in GVHD management among physicians. The intensity of GVHD management usually depends on physician's experience, beliefs, preference and patient/transplant characteristics. Whereas some transplanters are extremely concerned about GVHD and skeptical about the idea of manipulating it, others attempt to modify (titrate) it during its course and thus get the most out of it, because of its close association with the graft-versus-leukemia (GVL) effect. For example, some centers reporting to the IBMTR treat even stage I GVHD with systemic steroids in matched unrelated donor transplant setting because of the expected high incidence of GVHD in this group (G Vogelsang, personal communication).

As a consequence of these various approaches, transplant outcomes may vary. It is not uncommon to see the difference in GVHD practice among different attending physicians even within the same institution. In this paper, I have summarized several examples of current GVHD management strategies and discussed the concept of GVHD titration based on individual patient and transplant characteristics.

'A little bit of GVHD is actually a good thing' – an idea we all probably have conveyed to our patients during their initial consultation or at later visits. We tend to assure them by saying, 'It is desirable to see a little bit of GVHD after the transplant, because it may help to keep your leukemia away.' Most patients find this brief statement comforting. As reported by Horowitz *et al.*,¹ the risk of both relapse and overall treatment failure is low only in patients with mild graft-versus-host disease (GVHD): relapse rate is inversely and treatment failure is directly correlated with the severity of GVHD (Figure 1). The IBMTR and EBMTR data suggest that the best possible post transplant outcome is achieved in patients who develop mild GVHD.^{1,2}

Despite its widely accepted beneficial antitumor effect in many cases, the question of how we can induce and maintain GVHD without increasing morbidity and

Examples of GVHD titration

There has been a great deal of research interest in modifying the severity and course of GVHD. One of the earliest attempts was made in the late 1960s when the bone marrow product was preincubated with antigens and erythrocytes.³ With the introduction of modern immunosuppressive agents such as cyclosporin A in the late 1980s, GVHD could be prevented more effectively. Since then, we have acquired a better understanding of its pathophysiology, which led to the development of various effective regimens for preventing and treating GVHD. Although there has been progress in GVHD outcome, it still remains a major obstacle for a successful transplant. While waiting for more specific treatments to be available, we may be able to improve the survival outcome by optimizing GVHD management – that is, not over- or under-treating it (titrating GVHD).

There are plenty of examples of GVHD titration in our practice, though we may not recognize them as such. A good example could be the 'watch and wait' approach for grade I skin GVHD. We usually defer systemic corticoster-

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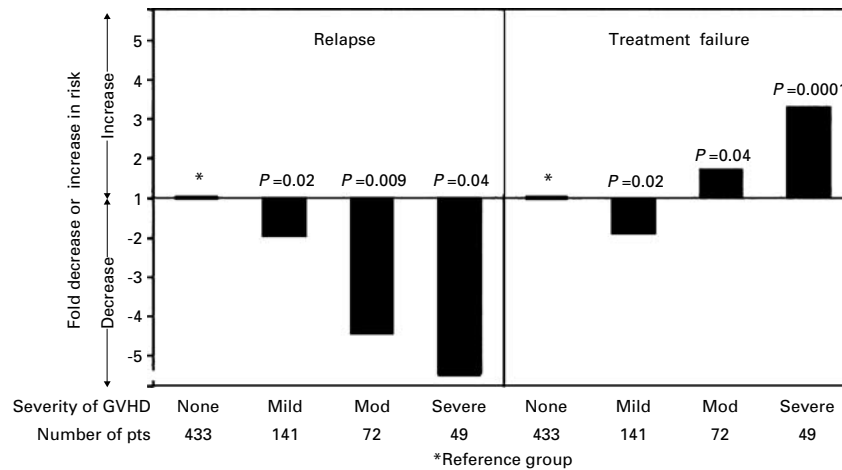


Figure 1 Risk of relapse and treatment failure after BMT for early leukemia with GVHD (by courtesy of Dr Mary Horowitz).

oid treatment until grade II or higher GVHD.²⁻⁴⁻⁶ Topical steroids are prescribed for symptomatic patients. Besides the overall grade of GVHD, timing of high dose systemic steroid administration also depends on the particular patient, underlying disease and transplant characteristics. Based on various clinical parameters, we can attempt to modify immunosuppressive therapy by holding off high dose systemic treatment if the patient's baseline characteristics suggest a low risk for GVHD and high demand for GVL. Close monitoring of the patient is mandatory to be able to do this.

Whereas some centers continue GVHD prophylaxis at full dose for 6 months, many others have adopted the practice of gradually tapering off immunosuppression, usually starting at 2 or 3 months after transplantation. It is generally recommended that patients with no documented GVHD decrease their cyclosporine or tacrolimus dose by 10–20% each week as long as they remain free of GVHD.⁷⁻⁹ The idea of gradual tapering of immunosuppression is based on the finding that engraftment, tolerance induction and conversion to full donor chimerism are usually complete by 3 months after myeloablative transplant. In most patients receiving a myeloablative conditioning regimen, acute GVHD occurs, if at all, within the first 2 months after transplantation.^{7,9} Therefore, once the direction of chimerism is confirmed by serial studies, tolerance and stable full donor chimerism are facilitated by withdrawing immunosuppression gradually for patients with no evidence of GVHD. This is a good example of titration/modification of immunosuppressive management. Gradual withdrawal of immunosuppression may also help with immune recovery and minimize side effects of the immunosuppressive medications.

The strategy of gradually tapering immunosuppression, allowing a gradual increase in donor chimerism without inducing severe GVHD, has been more widely accepted with non-myeloablative transplants. The dose and duration of immunosuppression have constantly been modified depending on chimerism and GVHD outcomes. For instance, if GVHD probability is high, patients receive a longer duration of cyclosporine and mycophenolate mofetil (MMF), as reported in recent studies from Seattle.^{10,11}

We can also titrate GVHD by modifying the dose of immunosuppression. We try to keep cyclosporine, tacrolimus, sirolimus and, most recently, MMF within a certain therapeutic range by serially measuring their serum levels.¹² Although the main purpose of drug-level monitoring after transplantation is to prevent possible drug-related toxicities, it can also be used to prevent severe GVHD precipitated by subtherapeutic drug levels.

Some transplant centers try to keep the tacrolimus level at the upper range or slightly higher than the recommended dose range for unrelated or mismatched transplant recipients, for whom the risk and severity of GVHD is higher than in comparable matched related recipients (J Ferrara, personal communication). This may be an indirect example of GVHD titration. In contrast, patients with high-risk leukemia such as primary refractory acute myeloid leukemia (AML) at the time of transplantation may be kept on the lower end of the recommended dose range even in the presence of mild stable GVHD. There is an increased risk of leukemia relapse with high-dose cyclosporin A after allogeneic bone marrow transplantation for acute leukemia.¹³ The idea of lowering the dose of immunosuppressive treatment is to enhance the potential benefit of the GVL/GVHD effect, which may be the only hope for long-term remission in these patients.

Use of a 'mini' dose of methotrexate has been introduced into clinical practice, as standard dose methotrexate was associated with severe mucositis with no significant improvement in GVHD incidence and severity.¹⁴ This suggests that GVHD can be prevented by using a different dose of the established medication. With this dose reduction, methotrexate-related toxicity could be reduced without losing its anti-GVHD effect. This suggests that attempts to optimize anti-GVHD approaches may result in improving overall transplant outcome.

Donor lymphocyte infusion (DLI) is another good example of manipulating/titrating GVHD.¹⁵ Patients usually receive a second DLI dose at a higher level if they do not develop GVHD after the first dose and still have evidence of disease. The goal of repeat DLI is to induce remission with acceptable GVHD. We tend to escalate DLI dose and adjust immunosuppression based on what we

consider to be the risk of relapse for each patient. This is particularly true for GVHD after DLI when the GVHD is allowed to smolder in an attempt to maximize the GVL effect. Similarly, preemptive T-cell infusion after T-cell-depleted allogeneic stem cell transplantation has been gaining popularity as a way of inducing GVL with minimal GVHD while also preventing rejection.¹⁶

Except in chronic myeloid leukemia (CML) in its chronic phase,¹⁷ the GVL effect is usually associated with full donor chimerism and clinically evident GVHD.¹⁸ In certain diseases, such as multiple myeloma, the intensity of GVHD may be important for inducing the anti-myeloma effect.^{18,19} Recent studies demonstrated that some malignant cells that survive even lethal doses of total body irradiation and chemotherapy given in preparation for allogeneic stem cell transplantation can be eliminated only by immunologically active donor cells.²⁰

Patients with advanced disease at the time of relapse, of course, may not respond to DLI even in the presence of severe GVHD, suggesting that the GVL ± GVHD may not be strong enough to eradicate the whole clone of malignant cells.²¹ We all know that the GVL-associated antitumor effect will never be more than modest: even with rip-roaring GVHD, some patients (outside the ‘good risk’ diseases – AML, CML, chronic lymphocytic leukemia, CR1) still have relapse, because cancer stem cells are usually resistant to induced cell death, whether by drugs, radiation or even T cells. GVL effect may only maintain the response achieved with novel treatment and eliminate the minimal residual disease with time.

Suggestions for GVHD titration

It may be possible to modify the course and severity of GVHD, at least in some patients, mostly by adjusting the dose and duration of immunosuppressive agents. The drug choice, dose, administration schedule and total treatment duration can be modified according to patients’ underlying disease, clinical characteristics and post transplant course. Many times, multiple modifications may be necessary.

In patients who are not in first complete remission or active disease at the time of transplantation, we would like to observe mild to moderate GVHD during their post transplant course. Because of their high risk of relapse after transplantation, we might consider delaying high-dose systemic corticosteroid administration until GVHD reaches overall grade II or higher levels or involves systemic organs (‘≥grade I liver and/or gut GVHD’). As is well established, disease recurrence can be precipitated inadvertently by administering high-dose corticosteroids for a prolonged period, which usually results in blockade of the beneficial GVL effect associated with GVHD.²² Therefore, the benefits and duration of GVHD therapies must constantly be balanced against the risk of GVHD and risk of relapse.

We all wish that GVHD, when it occurs, would not progress beyond grade I or grade II with skin only. Although we see a mild smoldering GVHD in some patients, others may suffer from rapidly progressing GVHD. The pace of progression indicates a poor prognosis in these patients. Therefore, some patients with early

Table 1 Examples of clinical predictors for relapse and GVHD

<i>Higher risk of relapse</i>	<i>Higher risk of GVHD</i>
Not in remission at the time of BMT	Unrelated or mismatched related donor transplant
Presence of poor cytogenetic abnormalities	Age > 50 years
Relapse within 1 year of last treatment	History of grade 4 regimen-related toxicity
More than two previous relapses before transplant	Total body irradiation-containing conditioning
Non-myeloablative conditioning	High number of T-cells infusion

Abbreviations: BMT = bone marrow transplantation; GVHD = graft-versus-host disease.

GVHD may need to be monitored closely without systemic treatment, or treated with a modest dose (1 mg/kg/day) of systemic steroid and their response monitored. Patients who have had a perfect human leukocyte antigen-match transplant are likely to respond to less intensive immunosuppressive treatment. In contrast, unrelated donor or mismatched related donor transplant recipients may require early intervention with systemic high-dose (≥2 mg/kg/day) corticosteroids, as the probability of severe GVHD is high in this group. A simple comparison of the total number of risk factors for relapse and GVHD in a particular patient may help in modifying the prevention or treatment methods for GVHD, for possibly better clinical outcomes (Table 1).

Each of these predictors will probably have different weight on particular outcome. Nonetheless, one of the two possible outcomes (relapse vs severe GVHD) would appear to be more dominant, depending on the distribution of risk factors in each patient profile. Sometimes, patients may have same magnitude of risk for relapse and GVHD. In those cases, the optimum approach could be prioritizing GVHD over relapse as GVHD is more imminent than relapse especially after myeloablative conditioning. Once the risk of GVHD decreases with time, additional modification in immunosuppressive prophylaxis may be necessary.

Using the clinical information, we may be able to plan the intensity and duration of immunosuppressive treatment during the pre- and post transplant periods. Of note, transplant recipients with non-malignant disorders, should receive maximum GVHD prevention and treatment all the time as we do not need GVL effect in this group of patients. Until we develop more precise tools to predict the occurrence of GVHD and measure its potential severity in each individual, we should continue to explore the possibility of controlling GVHD by using an algorithm to achieve a better clinical outcome. Comparative studies should be planned to test the hypothesis of such modified GVHD management that would improve outcome as compared to ‘fixed’ treatment modalities.

GVHD, even in mild degree may cause physical and emotional disturbances in some patients. The morbidity and quality of life with ongoing smoldering GVHD may not be acceptable for certain patients despite their underlying hematologic malignancies remain in remission. These and other consequences of GVHD modification attempts

should be discussed with the patient and the most optimum treatment strategy should be planned accordingly.

Conclusions

In summary, GVHD remains closely associated with a modest antitumor effect of donor effector cells in most hematologic malignancies. The major challenge in allogeneic transplantation is how to transfer allogeneic T-cell immunity without causing severe GVHD. There has been a great deal of interest over the past decade in separating GVHD and GVL. Investigators have put enormous effort into understanding the mechanism of GVL and developing specific treatment methods. While waiting for clinically applicable methods are available to separate GVL from GVHD, we probably need to learn how to live with GVHD in today's reality.

For now, the possibility of modulating the course and severity of GVHD in a more precise fashion remains simply an idea. One day, however, we might be able to order x units of GVL \pm GVHD for each individual with a particular clinical scenario and achieve better disease control. As most of us believe that GVL is a modest but potentially effective antitumor treatment and since it is usually associated with GVHD, why not attempt to utilize this immune-based treatment to the full for our patients? Until a reliable laboratory test (genotype profiling?) is developed for predicting the onset and potential severity of GVHD, we may develop a clinically relevant guideline to identify each individual's risk factors for GVHD and relapse. Risk-adapted prevention and treatment strategies may allow us to use GVHD/GVL as a crude but usually effective therapy for relentless diseases.

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